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Abstract

In this review we reflect upon our contributions to the study of the properties and mechanisms of long-term potentiation (LTP) and describe some of the major influences on our work. We then go on to consider whether LTP has fulfilled its early promise of providing a compelling account of the synaptic basis of learning and memory.

Background

Modern ideas about the biological basis of memory began with Santiago Ramón y Cajal, and the identification of the synapse as a discrete entity where one neuron can influence the excitability of another. Ramón y Cajal himself proposed that synapses were the sites at which memories were stored. This insight was subsequently formalized by Jerzy Konorski and Donald Hebb. Konorski introduced the term "synaptic plasticity" to describe the postulated strengthening of the conditioned pathway in classical conditioning (Konorski, 1948). Hebb's "neurophysiological postulate" asserted that coincident

presynaptic and postsynaptic activity resulted in the strengthening of the synaptic connection between the pre- and postsynaptic cell (Hebb, 1949).

At the beginning of the second half of the twentieth century neuroscientists with an interest in the neural basis of memory were engaged in a search for examples of long-lasting synaptic plasticity in monosynaptic—or at any rate well-characterized—neural pathways in the central nervous system. A favoured model for studying such changes in spinal pathways was post-tetanic potentiation (PTP), a transient increase in synaptic efficacy following tetanic (high-frequency) stimulation of the presynaptic neuron. However, PTP rarely lasted for more than a few minutes (Lloyd, 1949).

Others had been looking for examples of synaptic plasticity in the brain. One approach was to deliver trains of stimuli at 10 Hz or higher to the axons that project to the hippocampus. This resulted in a rapid increase in the number of target cells that fired action potentials as the train progressed, a phenomenon called ‘frequency potentiation’. While the efficiency of each stimulus in firing the target cells increased markedly during the train, the increased efficacy was again too short-lived, lasting only a few minutes, to be regarded as a potential mechanism of memory and learning (Gloor et al., 1964). Then, two years later, Terje Lømo described an increase in synaptically evoked responses in the dentate gyrus of the hippocampal formation that could last for hours following repeated high-frequency stimulation (Lømo, 1966).

Field potentials and LTP in the dentate gyrus

In the terminal region of perforant path fibres in the dentate gyrus, a perforant path volley elicits an initial negative-going synaptically generated population (or field) potential, followed by a positive-going spike reflecting the near-synchronous firing of granule cells (Figure 1A, B). The sizes of the population excitatory postsynaptic potential (field EPSP) and population spike reflect, respectively, the magnitude of the monosynaptic current generated by the perforant path volley and the number of granule cells discharged by that EPSP. The onset latency of the population spike indicates the time taken to reach the necessary threshold for spike discharge. Lømo began to study frequency potentiation in the dentate gyrus when he joined Per Andersen's laboratory at the

University of Oslo in 1964. He delivered trains of stimuli to the monosynaptic perforant path input to granule cells of the dentate gyrus and saw a persistent synaptic strengthening that increased with each episode of high-frequency stimulation before flattening out at a persistent elevated level. The population spike evoked by the first stimulus in each train increased in amplitude and appeared with progressively shorter latencies. These changes could endure long after the last tetanus. Lømo presented his findings at a meeting of the Scandinavian Physiological Society in Åbo, Finland in August, 1966 (Lømo, 1966; see also Lømo, 2018).

Figure 1 here

Work on other projects interrupted Lømo's experiments on the after-effects of high-frequency trains. In the autumn of 1968, Tim Bliss, who had a long-standing interest in the synaptic basis of memory, came to Andersen's laboratory to learn the technique of field potential recording. Over the following months Bliss and Lømo embarked together on a systematic examination of the phenomenon that Lømo had discovered two years before.

In their initial experiments on anaesthetized rabbits they used a bilateral design, with the perforant path input to dentate gyrus on one side of the brain receiving single test stimuli interrupted by high-frequency trains to induce potentiation, while the other side received only test stimulation. While Bliss and Lømo saw clear evidence of long-lasting potentiation with this design they were concerned that polarization effects produced by high frequency trains might enhance the efficacy of the stimulating electrode and thus account for the potentiation they observed. They therefore switched to a unilateral design in which tetanic stimulation was delivered by a second independent electrode to one of two pathways, as illustrated in Fig 1C, with the test electrode delivering constant test shocks to both control and test pathways throughout the experiment. A number of important properties of LTP emerged from these experiments (Bliss and Lømo, 1973):

• LTP involves both an increase in the synaptic response and an increase in neuronal excitability (later termed EPSP-to-spike or E-S potentiation).

• A series of tetani could cause progressive potentiation until a stable level was reached, which was unaffected by further tetani. Called saturation, this phenomenon is an example of what is now known as ‘metaplasticity’ (Abraham, 2008).

• Indirect evidence was obtained suggesting that LTP is restricted to the tetanized input and does not spread to other untetanized inputs to the same target cells (Bliss et al., 1973; Bliss and Lømo, 1973). This property is referred to as input-specificity.

• Contrary to a strict interpretation of Hebb's postulate, postsynaptic firing appeared not to be required for the induction of LTP. LTP could be obtained after tetanizing the perforant path with brief trains of stimuli at 100 Hz, a frequency at which a population spike was elicited by the first but not by subsequent stimuli in the train.

Subsequently, two key properties known as co-operativity and associativity were identified by Graham Goddard and colleagues. Co-operativity refers to the need to activate a threshold number of inputs (a threshold intensity for the induction of LTP had also been noted by Bliss and Gardner-Medwin.(1973) in the awake rabbit). At the behavioral level, co-operativity may serve to filter out non-salient information. Associativity refers to the property whereby a strong stimulus can enable a weak stimulus, that by itself is below threshold for LTP, to elicit LTP when the two independent pathways are activated together in close temporal and spatial proximity. This may form the synaptic basis of associative learning.

There was a relatively muted reaction both to the initial paper describing LTP in the anaesthetized animal (Bliss and Lømo, 1973) and, in experiments carried out later in London but published at the same time, to the demonstration that LTP could last for many days in the unanaesthetised animal (Bliss and Gardner-Medwin, 1973). It was not until a decade later that interest in the phenomenon exploded, first with the discovery that LTP in area CA1 requires binding glutamate to bind to postsynaptic N-methyl-D-aspartate receptors (NMDARs) by glutamate (Collingridge et al., 1983) and then that sufficient postsynaptic depolarization was required to remove the block of NMDARs by Mg^{2+} (Nowak et al., 1984), (Mayer et al., 1984). A further impetus was the demonstration that postsynaptic injection of calcium chelators could block the induction of LTP (Lynch

et al., 1983), These properties soon led to a molecular explanation for Hebbian synapses, as described below.

Bliss and Lømo (1973) concluded the discussion section of their 1973 paper by observing that 'while our experiments show that there is at least one group of synapses in the hippocampus whose efficiency is influenced by activity which may have occurred several hours previously, a time scale long enough to be potentially useful for information storage, whether or not the intact animal makes use of such a property in real life is another matter'. Today, LTP can be studied at every level from the purely molecular to the cognitive. Although definitive proof that the mechanisms of LTP subserve learning and memory in the behaving animal is still lacking, few neuroscientists doubt that such proof will eventually be forthcoming. Perhaps the most enduring legacy of the paper has been to provide an agenda that continues to drive the experimental exploration of the neural basis of memory.

Mechanisms of Induction

In the Fall of 1980, Graham Collingridge began a postdoctoral position in the laboratory of Hugh McLennan around the time that McLennan, Jeff Watkins and others, had identified multiple glutamate receptor subtypes - now known as NMDA, AMPA, kainate and metabotropic glutamate receptors. Collingridge, together with graduate student Steven Kehl, investigated the roles of the various glutamate receptor subtypes in hippocampal synaptic transmission and plasticity. When they applied NMDA locally to dendrites they observed a potentiation of the field EPSP which persisted for tens of minutes. Although not LTP, it was suggestive that there may be something about NMDARs and synaptic plasticity that was worth pursuing. Fortunately, Jeff Watkins has just made a potent and selective NMDAR antagonist, D-AP5 (or D-APV as it is sometimes known) and donated all he could spare (7 mg). But with iontophoretic administration this was sufficient to perform the crucial experiment, which revealed that blockade of NMDARs prevented the induction of LTP without appreciably affecting synaptic transmission or pre-established LTP (Collingridge et al, 1983). Subsequently, different classes of NMDAR antagonists, including those that block the channel or the

glycine site, were shown by Collingridge and others to reversibly block the induction of LTP.

The key next question was the identity of the glutamate receptor that mediated the potentiated synaptic response. Whilst NMDAR antagonists had little effect on the field EPSP evoked by low frequency synaptic transmission, compounds that additionally antagonized AMPA and kainate receptors reduced it significantly (Collingridge et al., 1983). As more selective α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) antagonists, such as the quinoaxalinediones, were developed, it became clear that AMPARs mediate the fast synaptic response (Andreasen et al., 1989; Blake et al., 1988). This led to a massive effort to understand how AMPAR-mediated synaptic transmission is modified - a subject to which we will return. But the question that was asked first was how do NMDARs trigger the induction of LTP?

The NMDA receptor has several unique properties: it is extremely sensitive to ambient levels of Mg^{2+} which block the ion channel in a highly voltage-dependent manner, it has a high permeability to Ca^{2+}, and relative to AMPAR-mediated responses it exhibits a synaptic response which has slow activation and decay kinetics. Collingridge showed how high-frequency stimulation engaged these properties and enabled the synaptic activation of NMDARs; the depolarization generated by the temporal summation of AMPAR-mediated EPSPs transiently removed the Mg^{2+} block (Herron et al., 1986) and enabled Ca^{2+} to enter into the postsynaptic spine (Alford et al., 1993). Crucial to the physiological activation of NMDARs was the transient reduction in GABA-mediated inhibition which otherwise served to hyperpolarize the membrane to intensify the Mg^{2+} block. Inhibition is particularly labile during theta patterns of activation, since this timing maximally activates a presynaptic GABA-B autoreceptor to depress GABA release (Davies et al., 1991).

This mechanism for the induction of LTP readily explains the hall-mark features of LTP; input specificity is due to the highly localized action of synaptically released L-glutamate that ordinarily does not spread to neighbouring synapses. Co-operativity is due to the need to activate multiple synapses to provide sufficient depolarization to remove the Mg^{2+} block. Associativity happens because sufficient depolarization can be provided by other pathways, including neuromodulators, that serve to augment the synaptic

activation of NMDARs (either by facilitating the depolarization necessary to alleviate the Mg^{2+} block or by modulating the conductance directly). Finally, the biophysical properties of NMDARs explain the Hebbian nature of LTP; presynaptic activity is required to provide L-glutamate to bind to NMDARs and postsynaptic activity is required to provide the depolarization to remove the Mg^{2+} block of NMDARs sufficiently for LTP to occur. It should be noted that postsynaptic firing (as postulated by Hebb) is one way to provide this depolarization due to the rapid Mg^{2+} unblocking kinetics but a subthreshold depolarization is also capable of doing so. The relative importance of firing vs subthreshold depolarization for Hebbian LTP under normal physiological conditions has not yet been established. The molecular explanation of the Hebbian synapse, based on the properties of the NMDA receptor, rapidly gained widespread acceptance and has featured in many review articles, including our own (Collingridge, 1985; Bliss and Collingridge, 1993).

Subsequent work, by many laboratories around the world, has shown that NMDARs are the major trigger for the induction of LTP in the central nervous system (CNS). But they are not the only ones. For example the mossy fibre pathway in the hippocampus does not require the activation of these receptors (Harris and Cotman, 1986), but rather utilizes metabotropic glutamate receptors (mGluRs; Bashir et al., 1993) and kainate receptors (Bortolotto et al., 1999). Also, some pathways utilize Ca^{2+}-permeable AMPARs (CP-AMPARs), which are AMPARs that lack the GluA2 subunit, to trigger LTP induction, as first demonstrated at spinal cord synapses (Gu et al., 1996). Additionally, CP-AMPARs can trigger LTP at synapses, such as at the Schaffer collateral - commissural pathway, where NMDARs serve as the primary mechanism (Jia et al., 1996; Plant et al., 2006; Park et al, 2016).

The diversity of synaptic plasticity mechanisms is further expanded by the existence of long-term depression (LTD). Low-frequency stimulation can reverse a potentiated response to baseline, when it is referred to as depotentiation (Staubli and Lynch, 1990), and, under certain circumstances, can induce LTD from a basal state, where it is commonly called *de novo* LTD (Dudek and Bear, 1992). These forms of synaptic plasticity also involve a variety of induction triggers, with NMDARs and mGluRs being the most prevalent forms, reviewed in (Collingridge et al., 2010). Significantly, LTP and

LTD co-exist at the same synapses, enabling precise bi-directional control of synaptic plasticity (Enoki et al., 2009).

Mechanisms of Expression

Whereas the mechanism of induction of NMDAR-dependent LTP rapidly gained widespread acceptance, the same cannot be said about the mechanism(s) of expression, i.e., what sustains the enhanced synaptic response. Space limitations prevent a full account of this extensive and controversial literature, much of which is discussed in a recent review (Bliss and Collingridge, 2013). In brief, what can be concluded is that three expression mechanisms, one presynaptic and two post-synaptic, have received strong experimental evidence:

- an increase in the probability of neurotransmitter release,
- an increase in single channel conductance of AMPARs
- an increase in the number of AMPARs.

In hindsight, this heterogeneity should come as no surprise given the multiple components of NMDAR-mediated LTP described below. It is likely that the different temporal components of LTP utilize different expression mechanisms.

Orthogonal to the pre vs post debate is a diverse body of research on the signaling pathways that link induction to expression. This topic, which we term LTP transduction, is another area of intense interest and controversy. Historically, the observation that some forms of LTP required protein synthesis came first, but soon after, a parallel body of work focused on the signaling pathways activated downstream of the NMDAR.

Protein synthesis-dependence of LTP

In the late eighties Klaus Reymann built up a lab in Hansjürgen Matthies' Institute of Pharmacology, and later in the Institute of Neurobiology Magdeburg. Reymann and colleagues started with a slice chamber from the University of California (Irvine), a gift from Gary Lynch's lab. They modified the chamber and identified appropriate experimental conditions to investigate LTP for more than the 10-60 min, which was the

common limit for *in vitro* experiments at this time. They were the first to observe that slices can be kept stable for > 10 hours and that augmenting the tetanization protocol from a single to three successive (spaced) trains at 100 Hz caused LTP to be expressed for a very long time (>10 h) (Reymann et al., 1985). This finding was a prerequisite for all subsequent *in vitro* work in the Reymann, and later Frey, labs on second messengers, non-glutamatergic transmitters and synaptic tagging. Although later studies revealed that a single tetanus can also lead to a persistent LTP lasting at least several hours (Bortolotto and Collingridge, 2000), the repeated train is commonly used to elicit sustained potentiation and, as described below, induces a mechanistically different form of LTP.

Several investigators had proposed the importance of protein synthesis for the formation of long-term memory. Matthies and others hypothesized that memory formation in the mammalian brain consists of distinguishable phases of short-term, intermediate, and long-term memory based on cellular mechanisms at the synaptic, synaptosomal, and nuclear levels (for review, see Matthies, 1989). If LTP is indeed a cellular mechanism for memory formation one could expect a similar dependence of LTP consolidation on protein synthesis. Matthies and his colleagues first demonstrated this in the pp-DG synapse *in vivo* (Krug et al., 1984) and later in the SC-CA1 synapse in hippocampal slices (Frey et al., 1988).

Supporting evidence came from the finding that the incorporation of radioactive-labeled amino acids into cytosomal proteins of hippocampal neurons is elevated for 1 h immediately after tetanization (see Reymann and Frey, 2007 for review). This transient enhancement of protein synthesis roughly coincides with the time window after tetanization during which the inhibition of protein synthesis with anisomycin prevents the generation of LTP. Regarding the site of protein synthesis, it seems that both dendritic and somatic compartments are involved (Reymann and Frey, 2007). The availability of these so-called plasticity-related proteins (PRPs) may reflect either translation of newly transcribed somatic mRNAs or translation of pre-existing mRNAs present in dendrites.

This left the conundrum of how somatically-translated proteins find their way to recently potentiated synapses. A synaptic tagging and capture (STC) hypothesis (Frey and Morris, 1997) proposed that, at the time of LTP induction, a local 'tag' is set whose role is

to capture these plasticity proteins, with the capture process triggering the stabilization of synaptic strength. Speculation regarding the biochemical nature of the tag has ranged from the temporary phosphorylation of one or more synapse-associated proteins, through specific molecules such as TrkB, to transient structural changes of dendritic spine morphology that are permissive for the entry of proteins to help stabilize the size-associated synaptic enhancement (Redondo and Morris, 2011). Another candidate for the synaptic tag is the CP-AMPAR (Plant et al, 2016). A key feature of the STC hypothesis is that the augmented availability of plasticity proteins is heterosynaptic such that tetanization of one pathway that induces protein synthesis-dependent LTP can provide the plasticity proteins used by an independent but weakly tetanized pathway to enable stabilization of its otherwise transient LTP. This idea has major implications for the retention of memory (see below).

Transcription-dependence of LTP

Experiments in the intact rat using translational or transcriptional inhibitors confirmed the requirement for protein synthesis, but suggested that gene expression was not necessary for the early maintenance of LTP in the dentate gyrus (Otani and Abraham, 1989). However, subsequent *in vitro* studies indicated that gene transcription may also be necessary within a few hours of induction (Frey et al., 1996; Nguyen et al., 1994). The discovery that immediate early genes (IEGs), many of which are transcription factors, were rapidly transcribed following induction of LTP (Cole et al., 1989; Wisden et al., 1990) further suggested the importance of transcriptional events, and indeed IEG induction is now widely used in optogenetic studies to define those neurons that have undergone an LTP-inducing event during hippocampus-dependent learning (Tonegawa et al., 2015; Choi et al., 2018). The importance of IEGs in LTP and learning was emphasized in a study of a mouse model in which the IEG zif268 was knocked out - short-term memory and initial LTP were intact but long-term hippocampus-dependent memory and long-lasting LTP were impaired (Jones et al., 2001). The genes activated by transcription factors, encoding proteins that are potential plasticity factors in the expression of LTP, are beginning to be documented (Chen et al., 2017).

Protein kinases and LTP

A question that attracted the attention of several groups beginning in the 1980s is what links the initial induction trigger (i.e. activation of NMDARs) with the expression mechanisms, principally the alteration in AMPAR mediated synaptic transmission. Reymann and others found early evidence for roles of calcium/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC) and protein kinase A (PKA), (Malinow et al., 1989; Matthies and Reymann, 1993; Reymann et al., 1988a,b). Subsequent studies found evidence for additional kinases (see Bliss et al., 2007, for details), but CaMKII, PKC and PKA remain the most extensively studied. The identification of roles for multiple kinases begs the question as to their relative roles. What has become clear is that the involvement of the different kinases varies according to the developmental stage of the animal, the synaptic pathway under investigation and the particular sub-type of LTP being investigated. For example, at Schaffer collateral-commissural pathway in adult rats, CaMKII is both sufficient and necessary for protein synthesis-independent LTP. (Malinow et al., 1989). PKA is additionally required for protein synthesis-dependent LTP, presumably because it triggers the *de novo* protein synthesis machinery (Frey et al., 1993).; In terms of PKC, a crucial discovery was that an atypical isoform (most probably PKMζ) is required to maintain protein synthesis-dependent LTP (Pastalkova et al., 2006). Interestingly, protein synthesis inhibitors can block the long-term increase in PKMζ, suggesting that PKMζ is a component of a protein synthesis-dependent mechanism for persistent phosphorylation in LTP (Osten et al., 1996). If an inhibitor of atypical PKC isoforms is applied after LTP, it is able to reverse LTP, potentially by interfering with the NSF-induced stabilization of synaptic AMPARs (Yao et al., 2008).

We now consider in more detail the three distinct components of NMDAR-dependent LTP that do not rely on gene transcription: STP, LTP1 and LTP2.

STP

The transient decaying phase of LTP is a robust phenomenon when high frequency stimulation is used. It is largely absent when pairing protocols are used to induce LTP, pointing to a pronounced frequency dependence of its induction. STP decays to baseline in approximately 20-40 min when interrogated with repetitive test pulses. Remarkably,

the decay of STP depends on synaptic stimulation and in absence of such stimulation can be stored for hours (Volianskis and Jensen, 2003). STP is therefore a misnomer; it is a form of LTP, the duration of which is shortened by activity. We have considered labelling it as such, but have decided here to retain the term STP since it is so entrenched in the literature. STP is a complex phenomenon, that involves at least two pharmacologically and kinetically distinct components (STP1 and STP2) (Volianskis et al., 2013). STP1 has faster decay kinetics than STP2 and involves the activation of different NMDAR subtypes: STP1 involves GluN2A- and GluN2B- containing NMDARs whereas STP2 involves GluN2B- and GluN2D- containing NMDARs. Available evidence suggests that STP is largely, if not exclusively, expressed by presynaptic mechanisms, involving an increase in the probability of transmitter release. Since it is readily induced by theta patterns of activity, it is logical to speculate that STP has important physiological roles, though this has barely been explored.

LTP1 and LTP2.

The labels LTP1 and LTP2 equate to the forms of LTP that are, respectively, independent of and dependent on *de novo* protein synthesis. These are frequently referred to as early-phase LTP and late-phase LTP (E-LTP and L-LTP, respectively) implying that protein synthesis is not required initially but is required at later stages, with the switch over occurring during a period of a few hours (for review, see (Reymann and Frey, 2007)). However, there are reasons to discontinue this terminology in favour of a revised version of the original nomenclature, as proposed by the Magdeburg group (see Reymann & Frey, 2007). LTP1 is of variable duration, lasting from one to many hours, depending on the induction protocol, and does not require protein synthesis. LTP2 is invariably long-lasting (many hours) and is protein synthesis-dependent. The critical factor that determines whether the potentiation comprises LTP1 or a combination of LTP1 and LTP2 is the timing (and potentially also the strength) of the induction trigger. When a single episode of high frequency stimulation (either applied as a tetanus or as theta burst stimulation) is delivered, or when several episodes are delivered in a short space of time (so-called compressed or massed stimuli), the resulting potentiation does not require protein synthesis (i.e., LTP1). But when the same stimuli are spaced in time (with inter-episode intervals of the order of minutes), a substantial component of the

potentiation then requires protein synthesis (i.e., LTP2). The requirement for protein synthesis occurs shortly after the second episode (Park et al., 2014), suggesting that the first episode primes the synapse for the rapid (i.e., within a few minutes) induction of the protein synthesis-dependent component. Note that LTP elicited by spaced stimuli elicits a mixture of protein synthesis-dependent LTP (LTP2) and protein synthesis-independent LTP (LTP1), as illustrated in Fig 2C). The existence of two potentially long-lasting forms of LTP can explain numerous conflicting data on the transduction and expression mechanisms of LTP. The relative roles of LTP1, LTP2, and transcription-dependent LTP3 in memory storage in the intact animal remain largely unexplored.

The priming trigger for LTP2 has been identified; it involves the transient insertion of CP-AMPARs (Park et al., 2016). These are inserted into the extrasynaptic plasma membrane by the first episode of high frequency stimulation (via a mechanism that requires NMDARs and PKA) and are driven into the synapse by the subsequent episodes of high frequency stimulation, by a mechanism that also involves NMDARs. The dwell time of CP-AMPARs in the plasma membrane probably explains the timing requirements of the induction of LTP2. Critical also for LTP2 is the activation of dopamine receptors (see below). In terms of expression mechanisms, the relative roles of presynaptic and postsynaptic changes for both LTP1 and LTP2 are still under debate (Bliss and Collingridge, 2013).

Figure 2 here

Metaplasticity

Metaplasticity is a term that refers to the plasticity of synaptic plasticity (Abraham, 2008). It encompasses a wide variety of different mechanisms by which plasticity can be modified. Metaplastic signals can occur before, during or after the induction trigger and may be modulatory (affecting the gain of plasticity) or permissive. Their actions may be restricted to the conditioned pathway (homosynaptic metaplasticity) or may act other neural pathways (heterosynaptic plasticity).

One of the most extensively studied forms of homosynaptic metaplasticity is triggered by the activation of mGluRs. These are a family of eight G-protein coupled receptors that regulate a variety of cell signaling pathways, including the activation of PKC, (group I)

and inhibition of cAMP (groups II and III). Motivated by understanding what triggers the activation of PKC in LTP, Reymann tested the effects of the first available mGluR antagonist (L-AP3) and found evidence for the involvement of mGluRs in the induction of LTP (Behnisch et al., 1991). Collingridge, with the medical chemists Watkins and Jane, then developed the first selective mGluR antagonists (notably MCPG), and confirmed and extended these findings (Bashir et al., 1993). They went on to show that mGluRs had a metaplastic function; they were sometimes necessary and sometimes not for the induction of LTP, a critical factor being the prior history of the synapses (Bortolotto et al., 1994). Specifically, it was found that prior activation of mGluRs led to an additional form of LTP that was independent of mGluRs. A different manifestation of the same mechanism was observed independently by Abraham and colleagues. Notably, they found that the mGluR-primed form of LTP required *de novo* protein synthesis whereas the unprimed form did not (Raymond et al., 2000). Returning to PKC, inhibitors of conventional PKC isoforms were found to selectively block mGluR-triggered metaplasticity (Bortolotto and Collingridge, 2000). The existence of these two mechanistically distinct forms of LTP (unprimed and primed), which may relate to LTP1 and LTP2, respectively, could partly explain the earlier controversies surrounding the roles of both mGluRs and kinases in this process.

Another factor that may determine the involvement of mGluRs in the generation of LTP is the strength of the induction trigger (Wilsch et al., 1998). A potential mechanism is provided with the finding that activation of mGluRs can potentiate NMDAR function (Fitzjohn et al., 1996) possibly via the regulation of SK channels (Tigaret et al., 2016). In other words, with a relatively modest stimulus, co-activation of mGluRs and NMDARs is required to reach the LTP threshold whereas with a strong stimulus NMDARs alone are sufficient. Clearly, mGluRs add an additional level of complexity to LTP, the purpose of which may be enable synaptic activity patterns to effect homosynaptic neuromodulation (i.e., metaplasticity).

These studies focussed on the early involvement of mGluRs in synaptic plasticity and metaplasticity. However, Reymann and colleagues went on to show an involvement of mGluRs in long-lasting LTP in area CA1 and the dentate gyrus of freely moving rats (Manahan-Vaughan et al, 1997) (Manahan-Vaughan et al., 1998). For a more detailed

account of the functions of mGluRs in synaptic plasticity, metaplasticity and learning and memory see Manahan-Vaughan et al (2018, this volume).

Saliency signalled by monoamines

Essential heterosynaptic metaplasticity is provided by the classical neuromodulators. A critical function for the nervous system is to decide what information is important to store and what can be quickly ignored or discarded. This saliency is believed to be determined, in part, by the actions of the monoamines neurotransmitters, in particular noradrenaline (NA), dopamine and 5-HT. In terms of the cellular substrate of saliency, there has been interest in how these neuromodulatory agents impact upon LTP. This was first addressed by Bliss, Goddard and Riives, who showed that LTP at perforant path synapses in the dentate gyrus required both 5-HT and NA projections for its full expression (Bliss et al., 1983). Reymann similarly found a requirement for NA, acting via beta receptors, for the formation of long-lasting LTP at these synapses (Seidenbecher et al., 1997).

Dopamine is also required for memory consolidation in some learning tasks (Matthies, 1989, 1990). Pertinent to this, Reymann's lab found evidence that dopamine is important for the generation of long-lasting LTP in the CA1 region of hippocampal slices (Frey et al., 1990; (Reymann and Frey, 2007). In these experiments, either dopamine D1/D5 antagonists or PKA inhibitors blocked the protein synthesis-dependent form of LTP (i.e., LTP2). The induction of LTP2 in CA1 apical dendrites may therefore require an obligatory activation of heterosynaptic inputs from catecholamine terminals. Thus the induction of LTP2 may not be purely glutamatergic; rather dopamine (in CA1 apical dendrites) and NA (in the dentate gyrus) seem to have a permissive function similar to behavioral reinforcement for memory consolidation (Frey et al., 1990); (Seidenbecher et al., 1997). An intriguing twist was added by Morris and colleagues who showed that the activation of the locus coeruleus (LC) facilitated hippocampal LTP, but paradoxically utilized dopamine, rather than NA, as the reinforcer (Takeuchi et al., 2016). Further work is required to establish the extent to which these classical neuromodulators are required for LTP2 and the associated learning and memory processes and to what extent these and related roles are also performed by other monoamines and by acetylcholine.

Relationship of LTP to learning and memory

The discovery of LTP and progress in understanding its neural mechanisms of induction, expression and maintenance of distinct forms of LTP (LTP1 and LTP2) left open the further but logically separate issue of the function of synaptic plasticity within the brain. The original paper of 1973, in its concluding paragraph, alluded to a potential role in learning (Bliss and Lømo, 1973). While synaptic potentiation may serve diverse functions in various brain areas (Bliss et al., 2014), a key issue has been: “Does LTP play a role in learning?”.

Three groups were the pioneers in taking forward research on LTP and memory. The first was that of Graham Goddard and his students Rob Douglas, Carol Barnes and Bruce McNaughton, working at Dalhousie University in Canada, who formalized the concepts of co-operativity and associativity - two of the defining characteristics of LTP noted above. In behavioral studies, Barnes and McNaughton investigated whether alterations in memory associated with aging might be understood, at least partly, in terms of an altered capacity for LTP. They showed that the decay of LTP over days correlated with forgetting of spatial memory tested in an ingenious “find the burrow” task that is now widely used as the Barnes Maze (Barnes, 1979; Barnes and Mc Naughton, 1985). Barnes’ subsequent career has focused on diverse facets of the electrophysiology of aging, revealing numerous important insights - notably to do with age-related compensation in synaptic transmission and plasticity (Burke and Barnes, 2006). The second was the group in Magdeburg in the then German Democratic Republic, led by Hansjürgen Matthies, which began studying LTP both *in vivo* and *in vitro*, and investigated whether LTP expression was in any way linked to various learning tasks that the group were studying. The concept of multiple stages of LTP and memory was described by Matthies and his colleagues in an important review in Advances in Experimental Medicine in 1990, published just as the tumultuous events that were to lead to the end of GDR engulfed the country (Matthies et al., 1990).

The third group to become interested was that of Richard Morris, following Collingridge’s observation of an essential role for NMDARs in LTP induction (Collingridge et al., 1983).

Morris was, at the time he first learned of this work from Eric Harris, on a sabbatical visit to Gary Lynch's laboratory in Irvine, California where his group had been testing a calpain inhibitor drug called leupeptin - which turned out to have only modest effects on memory. Collingridge's LTP data were striking, and were complemented by supportive work in another laboratory in Irvine (Harris et al., 1984). Morris resolved to return to St Andrews and try out AP5 (a gift from Jeff Watkins) in both *in vivo* physiology and behavior studies. Initially using D,L-AP5, later D-AP5, Morris found that drug infusion directly into the lateral ventricle over 14 days using osmotic minipumps caused an impairment in the learning of a well delineated hippocampus-dependent task - spatial learning in a watermaze - at a dose that also blocked LTP induction (Morris et al., 1986). Intrahippocampal microinfusions had the same effect. Control studies revealed some specificity of the learning impairment, as a procedural visual discrimination learning task was unaffected; this was comforting as this task is also left unimpaired by lesions of the hippocampal formation. These studies were followed by work showing that NMDAR-blockade *after* learning had no effect on memory retrieval, and by dose-response studies revealing a commonality between the extracellular concentrations of D-AP5 that are effective behaviorally *in vivo* and those that blocked LTP *in vitro* (Davis et al., 1992). Further studies in Edinburgh investigated the contribution of other glutamate receptors to LTP induction and memory encoding (e.g. mGluRs). A foray into using Thy-1 knock-out mice (Nosten-Bertrand et al., 1996) initially threw up the theoretically exciting but challenging observation that spatial learning was unimpaired by a genetic deletion that apparently blocked LTP in the dentate gyrus of anaesthetised rats. However, later work indicated that this was likely due to an effect of the gene knockout on inhibitory neurons because LTP could be observed in the freely-behaving awake animal (Errington et al., 1997).

A step forward in behavioral analysis was Morris and others' growing appreciation that the intrinsic neuroanatomical circuitry of the hippocampus was ideally suited to the initial encoding of "episodic-like" memory - the "what, where, when" of memory for single-events. Achieving this tri-partite representation is difficult and few studies have yet achieved it to date. However, his group put effort into designing improved behavioral paradigms for investigating episodic-like memory (Day et al., 2003; Steele and Morris, 1999). In the watermaze and event arena respectively, they developed a task in which new spatial learning and memory could be observed each day after minimal training (as

little as one trial), with daily training of different locations continuing across days, weeks and even longer. Both paradigms revealed deleterious effects of D-AP5 on memory encoding after a single-trial of these episodic-like tasks. This finding was followed up by a study from Tonegawa's group that showed "one-shot learning" to be blocked by a CA3-specific knockout of NMDARs in mice (Nakazawa et al., 2003).

Criteria for testing the synaptic plasticity and memory hypothesis

Morris, with his then Ph.D student Stephen Martin, suggested various criteria that we judged might be helpful for rigorous testing of the synaptic plasticity and memory (SPM) hypothesis (Martin et al., 2000). The existence of different forms of LTP (LTP1 and 2) were recognized, but so also was that of different forms of learning and memory mediated by different brain areas and network. One synaptic plasticity criterion was that any treatment (physiological, pharmacological or genetic) that limited the induction of synaptic potentiation in a brain area should have a complementary and anterograde effect on the type of learning mediated by that brain area. For the hippocampus, and separately the amygdala, this criterion was met. For example, in the hippocampus *prior* saturation of LTP impaired new memory encoding (Castro et al., 1989; Moser et al., 1998), by Morris and other groups' pharmacological studies (above), and by region-specific gene knock-out studies in mice (Tsien et al., 1996). Another criterion was that attempted saturation of LTP induction *after* prior learning should retrogradely impair the accuracy of memory retrieval. This criterion was also met (Brun et al., 2001). A fascinating new twist on this retrograde theme has been Kasai's recent demonstration that selective genetic ablation of synapses in motor cortex that were potentiated during the learning of a motor task is sufficient to cause memory disruption, whereas ablating those associated with a different motor task should and did have little effect (Hayashi-Takagi et al., 2015). Potentially, this selectivity is a striking example of synaptic rather than cellular specificity (see below). A third criterion was that the creation of memory traces by learning should be accompanied by measurable changes in synaptic strength in the appropriate brain area. After a number of failed attempts, this "needle-in-the-haystack" criterion was also met for both hippocampus and amygdala, using both multiple electrode recording within individual animals (to find the "needle") and AMPAR trafficking as measures of potentiation (Rumpel et al., 2005; Whitlock et al., 2006). The

last criterion was that of mimicry. The idea here is that if a memory trace is a spatially distributed array of both stable and modified synapses, then the artificial creation of just such a pattern should create an equally artificial memory of something that, in practice, had not happened. This criterion has not yet been realized. However, approximations to mimicry have been developed, such as work by the Malinow group who showed that, once an animal had acquired a conditioned fear response (displayed as a decrease in lever-pressing in a conditioned suppression operant task), application of suitable optogenetic LTP-inducing or LTD-inducing stimulation on relevant amygdala pathways could increase or decrease the strength of the memory (Nabavi et al., 2014). This approach does not work if the animal has not previously been trained, and so fails a strict interpretation of the mimicry test. However, it is intriguing that the fear memory can be artificially increased or decreased by appropriate neural activation. Moreover, input-specific LTP underlies the selective behavioral responses observed to conditioned stimuli (Bocchio et al., 2017)

Engrams: cellular or synaptic?

Beyond these studies, a potentially exciting new approach is the concept of “engram cells”. This is clearly Hebbian in spirit as the idea that an ensemble of cells reflects or even mediates a memory trace, i.e. an engram, is consonant with Hebb’s concept of a “cell-assembly”. What is less clear is whether the subset of cells of a brain area within such an assembly have a specific and "branded" (so to speak) role in one memory, while other but possibly overlapping cells mediate a different memory (engram 1, engram 2, etc.). The alternative is that the engine-room of specificity lies in input-specific synaptic potentiation, synaptic depression or synaptic stability given the multiple synaptic connections on excitatory neurons and thus massively greater storage capacity. On this view, an individual cell would be expected to be involved in many different engrams, but a specific spatial pattern of LTP/LTD on multiple cells would still have a one-to-one relationship to a single engram.

An ingenious technique that has been developed to investigate engram cells involves first marking, on the basis of cFos activation during memory encoding, a subset of cells that thereafter express channelrhodopsin (ChR2). This is achieved by infusing a cre-

dependent ChR2 virus into a brain area and using a cFos-cre line of animals. The juxtaposition of these two realizes cell specificity. The next step is to optogenetically activate this subset of cells that may constitute part or all of the 'engram' (Josselyn et al., 2015, 2017; Tonegawa et al., 2015). From the perspective of those who see synaptic plasticity as the prime mediator of memory formation, such an approach is a little indirect. Its power, however, resides in the technically sophisticated possibility of investigating the causal role of a putative memory-related subset of neurons in a given brain region in a manner that has not been possible before. The Tonegawa lab has shown, for example, using hippocampus-dependent context-fear conditioning, that animals which first receive optical activation of ChR2-labelled neurons in the dentate gyrus corresponding to context A, and then receive an electric shock in context B during a period in which the engram cells of context A are also light-activated, go on to display freezing in context A when returned to it later. That is, a fear engram ensemble is created that can be contextually activated by context A cues even though fear conditioning never actually occurs in context A. This approach is yielding new insights into false memory and valence reversal.

However, the approach may run into difficulty when the studies extend beyond context fear conditioning, and beyond induction and expression to the issue of memory retention over time via consolidation. Specifically, Tonegawa has queried whether synaptic potentiation can be the whole story for memory retention on the basis that a context-fear memory could be successfully activated by light even when synaptic potentiation has decayed to the point where it could no longer be activated by the usual environmental triggers - whether this trace decay had happened naturally over time or following the application of a protein synthesis inhibitor (Kitamura et al., 2017). Kitamura et al's (2017) data reveal that stimulation by light of the ChR2-labelled engram cells reactivates the freezing response even though synaptic potentiation has ostensibly decayed to baseline and environmental triggers don't work. This is a challenging finding for the synaptic plasticity hypothesis. The analysis of LTP1 and LTP2 we have presented in this review offers one potential solution to this puzzle. We argue that LTP2 depends on protein synthesis, but LTP1 does not. One way of thinking about the dissociation between lasting components of LTP and of memory would be to suppose that it is LTP1 at the connections between hippocampus and amygdala which mediates the freezing response (through plasticity at amygdala synapses), whereas learning about contextual

cues is encoded by LTP2 in the hippocampus. In animals treated with anisomycin the ensemble cells encoding place become loaded with ChR2 and can thus be activated by light, even though the animal has forgotten the place, and mediate freezing via LTP1 in the still potentiated hippocampus-amygdala projection. Anisomycin-sensitive LTP2 in the afferent inputs to hippocampus encoding context would decay and so no longer elicit freezing.

As mentioned above, many view an engram not as a group of interconnected neurons that are activated during a memory but rather as the set of alterations in synaptic weights within an activated neuronal population. Memory capacity is greatly expanded when information is stored as synaptic weights rather than as neuronal assemblies - there being approximately 1,000 times more synapses than neurons and a vastly greater number of combinations of synaptic weights than of neurons in any given cortical network. This more Hebbian view of the engram has recently gained strong experimental support from the development of novel optical and genetic techniques. Firstly, it was shown that motor learning involves synaptic remodelling in a subset of neurons and, importantly, that the memory could be disrupted if the potentiated spines within this ensemble were specifically shrunk (Hayashi-Takagi et al, 2015). Secondly, Kaang and colleagues have recently studied the synaptic engram encoding a context-dependent fear conditioning task and reported that commissural CA3 to CA1 synapses were anatomically larger and functionally stronger when they connected neurons that were activated during learning, as labelled by the immediate early gene cfos. This strengthening appears to be due to synaptic potentiation, since LTP after learning was saturated when it involved synapses between participating neurons (Choi et al, 2018).

Protein synthesis-dependent LTP, engram cells and memory retention

The combination of different forms of LTP, network connectivity, and uncertainty about how long the cFos:cre-dependent marking with ChR2 itself lasts over time adds to the difficulty of interpreting the challenging Kitamura et al (2017) findings. Resolving this discrepancy may indeed reveal other components of memory mechanisms beyond those mediated by LTP1, LTP2 (or even LTD), but, if so, their functional role will also require

confirmation in other tasks beyond context fear conditioning as used exclusively in the 'engram cell' work to date. LTD may also be relevant to limiting the saturation of LTP, and its induction in behaving animals can also arise as a consequence of exposure to novelty (Manahan-Vaughan, 2018, this volume). One intriguing issue relevant to memory retention is that changing the timing of memory encoding trials in the event arena, from massed (every 30 sec - which would trigger LTP1) to spaced (every 10 min, sufficient to trigger LTP2) was recently observed to have not only the long-documented positive effect on spatial memory retention but also a dramatic effect on gene transcription, identified using RNAseq (Nonaka et al., 2017).

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Related to the pioneering work of the Magdeburg group and early studies in the Bliss lab, recent research has re-examined the place of neuromodulatory transmission in LTP and memory. Frey and Morris (1997) observed that protein synthesis-dependent LTP2 could be induced during the inhibition of protein-synthesis using a two-pathway design that enabled the putative PRPs upregulated by tetanization on one pathway to be shared with another pathway tetanized in the presence of anisomycin (Frey and Morris, 1997). They referred to the likely underlying principle as 'synaptic tagging and capture' (STC; see above). Further studies have shown that synaptic tags can be reset by rapid depotentiation (Sajikumar and Frey, 2004b), and that there may be some sharing of the PRPs upregulated by LTP-and LTD-inducing stimulation now referred to as 'cross-tagging' or perhaps more correctly as 'cross-capture' (Sajikumar and Frey, 2004a). Tonegawa's group has also shown STC at the single-cell level (Govindarajan et al., 2011). Examining the behavioral relevance of STC (Morris and Frey, 1997). Hydee Viola's group in Buenes Aries introduced the idea of "behavioral tagging" whereby the retention of a weak memory, or one induced in the presence of anisomycin, could be enhanced by other behavioral experience that likely activated PRPs such as novelty (Moncada and Viola, 2007). Independently, Morris's group showed that brief (5 min) post-encoding novelty (30 min after encoding) enhanced spatial memory retention at 24 hr for a task that was ordinarily forgotten within a day (Wang et al., 2010). This so-called 'everyday memory' paradigm (i.e. the study of memory traces that are in long-term memory but last less than a day) was sensitive to blockade of D1/D5 receptors in the hippocampus. Using the tyrosine hydroxylase (TH):cre mice, post-encoding optogenetic activation of the LC with a light pattern modelled on what was seen in TH+ neurons in response to environmental novelty had the same synergistic effect (Takeuchi et al.,

2016). Additional studies of both sufficiency and necessity pointed to an important neuromodulatory role of arousal, mediated by the LC, in enhancing memory retention. Interestingly, the effect was also observed *in vitro* in which a similar optogenetic light pattern enhanced hippocampal EPSCs and LTP. Both the *in vivo* memory retention findings and the *in vitro* physiological enhancement were, paradoxically, sensitive to a blocker of D1/D5 receptors in hippocampus rather than noradrenergic blockade. This may reflect the release of dopamine from NA terminals (Kempadoo et al., 2016).

Conclusions

We have told the tale of LTP, largely through personal reflection, from its earliest beginnings through to its diverse complexities in contemporary studies, with respect to its induction, expression and maintenance. We also noted that there is now very strong evidence that an LTP-like mechanism mediates at least some aspects of memory. A key message is that recognition of distinct types of long-lasting synaptic potentiation helps to resolve a number of current disputes. One type, STP, decays very quickly when it is expressed, but the short-term nature of STP can nonetheless be stored latently for a long time. LTP1 and LTP2, as we have defined them, are both long-lasting, though LTP1 is probably not invariably so, and only LTP2 requires the synthesis of plasticity-related proteins thought to sustain the structural changes associated with LTP expression. The functional significance of transcription dependent LTP3 has barely been explored. One challenge ahead is to discover how the different patterns of stimulation required to induce these forms of potentiation are mirrored in the intact brain during learning.

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Glossary

AMPAR – α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor
CA1 – cornu ammonis, subregion 1
LTP – long-term potentiation (for subtypes 1,2,3 see text and figure 2)
LTD – long-term depression
NMDAR – N-methyl-D-aspartate receptor
CaMKII - calcium/calmodulin-dependent protein kinase II
ChR2 - Channelrhodopsin
c-fos – a proto-oncogene widely used as immediate early gene marker
CP-AMPAR - calcium-permeable AMPA receptor
cre - cyclic AMP response element
cAMP - cyclic-adenosine monophosphate
D1 - Dopamine receptor subtype 1
D5 - Dopamine receptor subtype 5
D-AP5 - D-2-aminio-5-phosphonopentanoic acid
DG - Dentate gyrus
EPSC - Excitatory postsynaptic current
EPSP - Excitatory postsynaptic potential
IEG - Immediate early gene
GluA2 - Glutamate receptor AMPA receptor subunit 2
GABA - γ -aminobutyrate
5-HT - 5-hydroxytryptamine
mGluR - metabotropic glutamate receptor
L-AP3 - L-2-amino-3-phosphonopropionat
LC - Locus coeruleus
MCPG - methyl-4-carboxyphenylglycine
NA - Noradrenaline
NSF - N-ethylmaleimide-sensitive fusion protein
NO - Nitric oxide

PKA – Protein kinase A

PKC - Protein kinase C

PKM - Protein kinase M

pp - perforant path

PRPs - Plasticity related proteins

RNAseq – Ribonucleic acid sequence

SC - Schaffer collateral

SK - small conductance calcium-activated postassium channels

SPM - Synaptic plasticity and memory

STC - Synaptic tagging and capture

STP - Short-term potentiation

TH+ - Tyrosine hydroxylase positive

Thy-1 – thy-1 cell surface antigen

zif268 – zinc finger protein 225

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Legends:

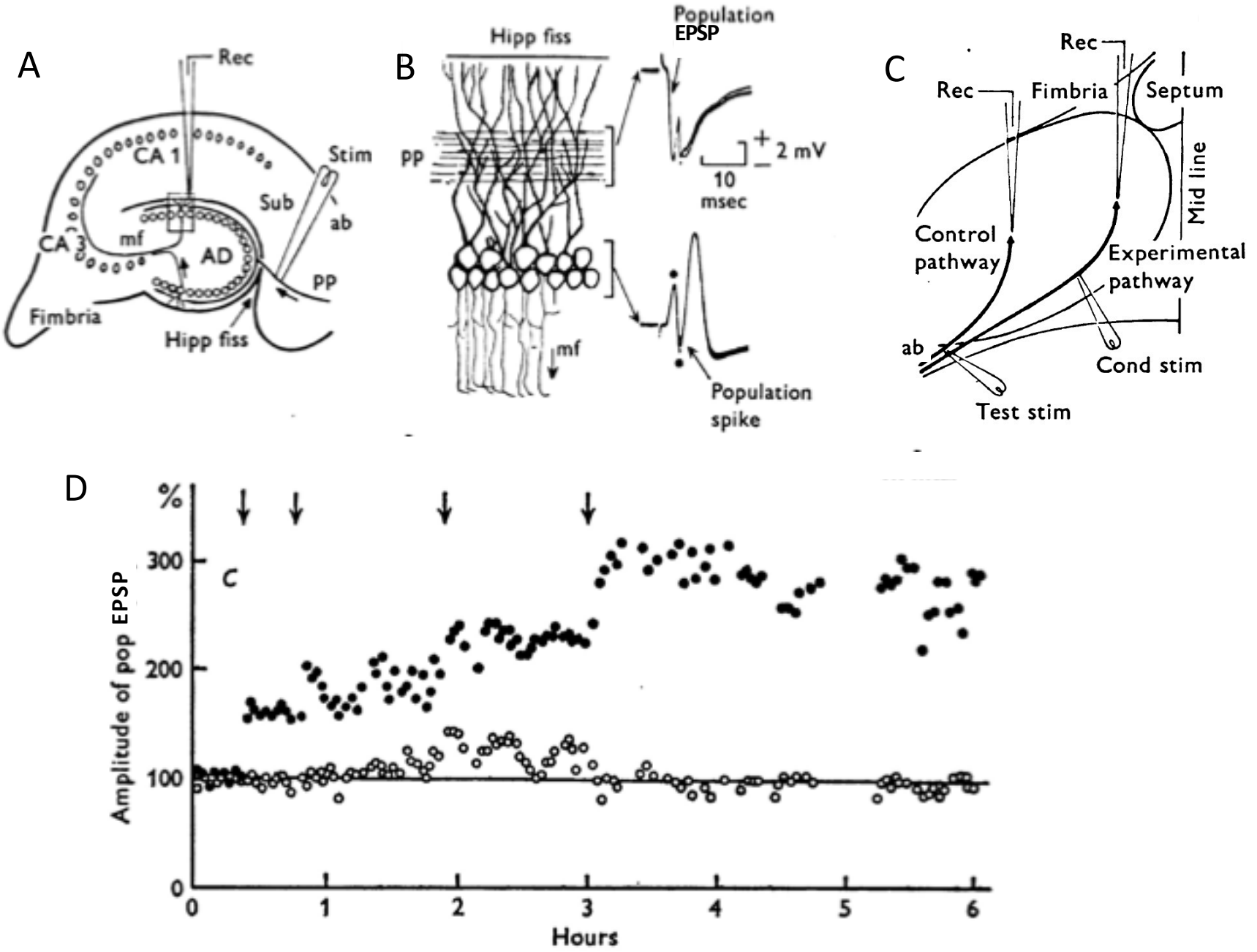
Figure 1: An example of long-term potentiation from the first detailed study of the phenomenon.

Long-term potentiation in the dentate gyrus of the anaesthetized rabbit. A-C. Anatomy of the hippocampus (A), population potentials from synaptic and granule cell body layers (B), and placement of stimulating and recording electrodes (C). The arrangement of the two stimulating electrodes in (B) allowed the rostral electrode (Test stim) to activate the perforant path in the angular bundle before it fans out to innervate the rostro-caudal extent of the dentate gyrus, while the second conditioning electrode (Cond stim) was placed more rostrally to activate only fibres projecting to granule cells nearer the midline (experimental pathway). Test stimuli were given via the caudal stimulating electrode at a constant rate (15/min) throughout the experiment, and responses averaged. Recording electrodes were lowered into the terminal zone of medial perforant path fibres in the molecular layer of the dentate gyrus, at two positions, defining the control and experimental pathways (B). High-frequency trains (15Hz for 15 sec) were delivered at intervals to the experimental pathway (arrows in D) via the conditioning stimulating electrode. D. Long-term potentiation of the population (field) EPSP in the experimental pathway (filled circles) but not the control pathway (open circles) pathway following multiple episodes of high-frequency stimulation (adapted from Bliss and Lømo, 1973). Abbreviations: ab angular bundle, pp perforant path, sub subiculum.

Figure 2: Multiple components of NMDAR-dependent LTP at Schaffer collateral-commissural synapses.

A. The four phases of synaptic potentiation as originally defined by the Magdeburg group (adapted from Reymann & Frey, 2007). LTP1 is defined by sensitivity to kinase inhibitors (originally PKC inhibitors) but not protein synthesis inhibitors; LTP2 by sensitivity to translational but not transcriptional inhibitors and LTP3 by sensitivity to transcriptional inhibitors. If none of the four components is blocked a full, long-lasting LTP will be established (top black line). STP is largely resistant to these inhibitors.

B, C. A revised terminology for the stages of LTP: B. The decay of STP is rapid during activation of the potentiated pathway. However, STP can be stored in latent form for many hours in the absence of activation and can therefore be considered a form of LTP (adapted from Volianskis and Jensen, 2003). C: A pairing protocol (top trace) selectively induces LTP1 (the pairing frequency is too low to induce STP). A compressed induction protocol (including a single tetanus) induces STP and LTP1; it is dependent on protein kinases, but independent of protein synthesis. The duration of LTP1 is variable; under certain conditions (e.g., a weak tetanus), LTP1 decays within an hour or so and is then commonly referred to as E-LTP (dashed line), but following stimulation with compressed trains or a single strong tetanus LTP1 can last for several hours. A spaced protocol triggers LTP2, a long-lasting potentiation that requires protein synthesis and is additive to LTP1. Note that it is induced very rapidly following the second induction stimulus when the inter-train interval is of the order of minutes. The total LTP induced by spaced protocols is commonly referred to as L-LTP (a composite of LTP1 and LTP2); the blue trace shows the residual potentiation (i.e., LTP1) achieved when spaced trains are given in the presence of a protein synthesis inhibitor. The arrow(s) depict the induction stimulus (e.g., high frequency stimulation or theta burst stimulation). Note that the relation between the E-LTP and L-LTP and the revised terminology of LTP1,2 and 3 presented here needs further investigation.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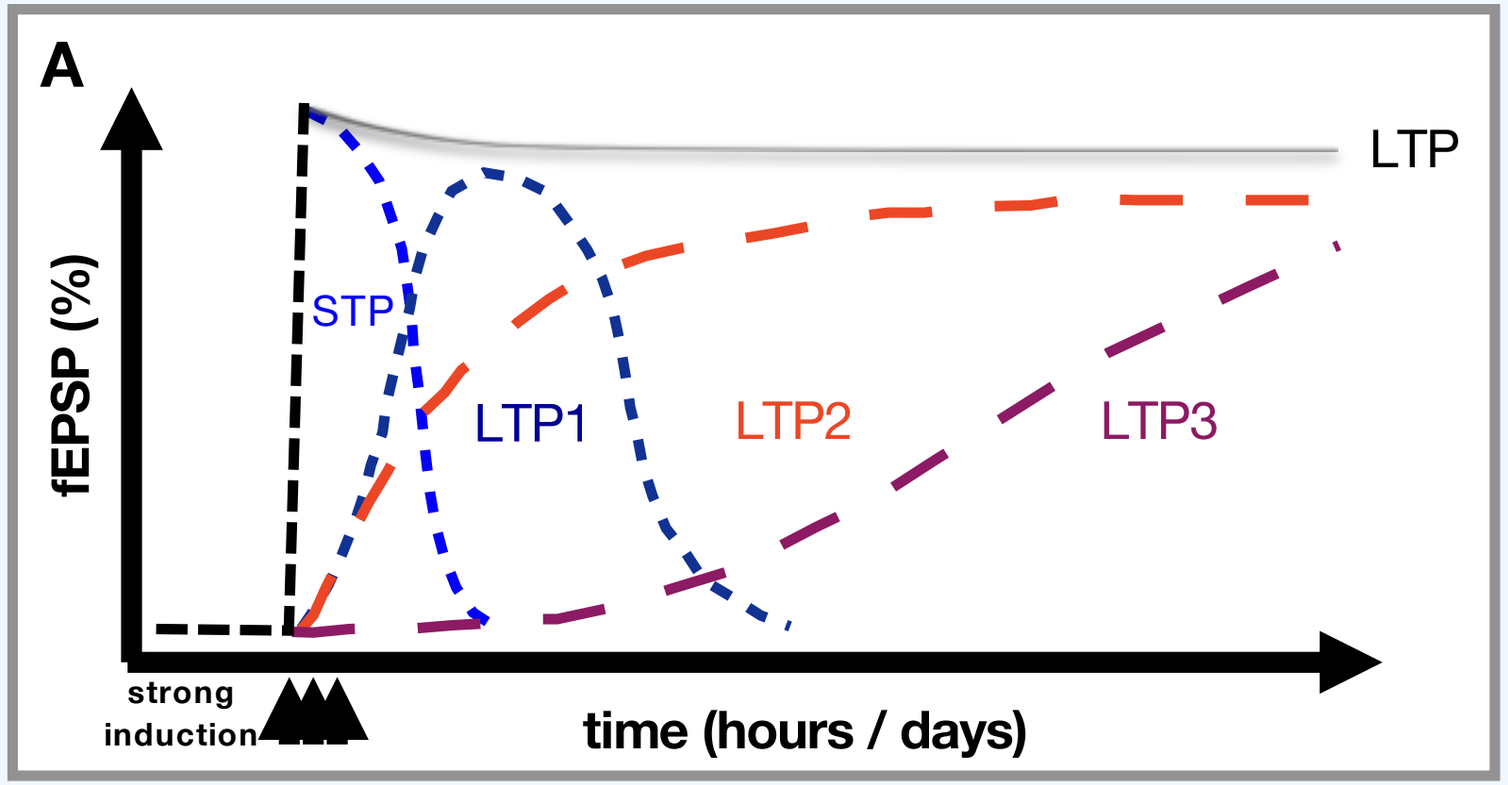
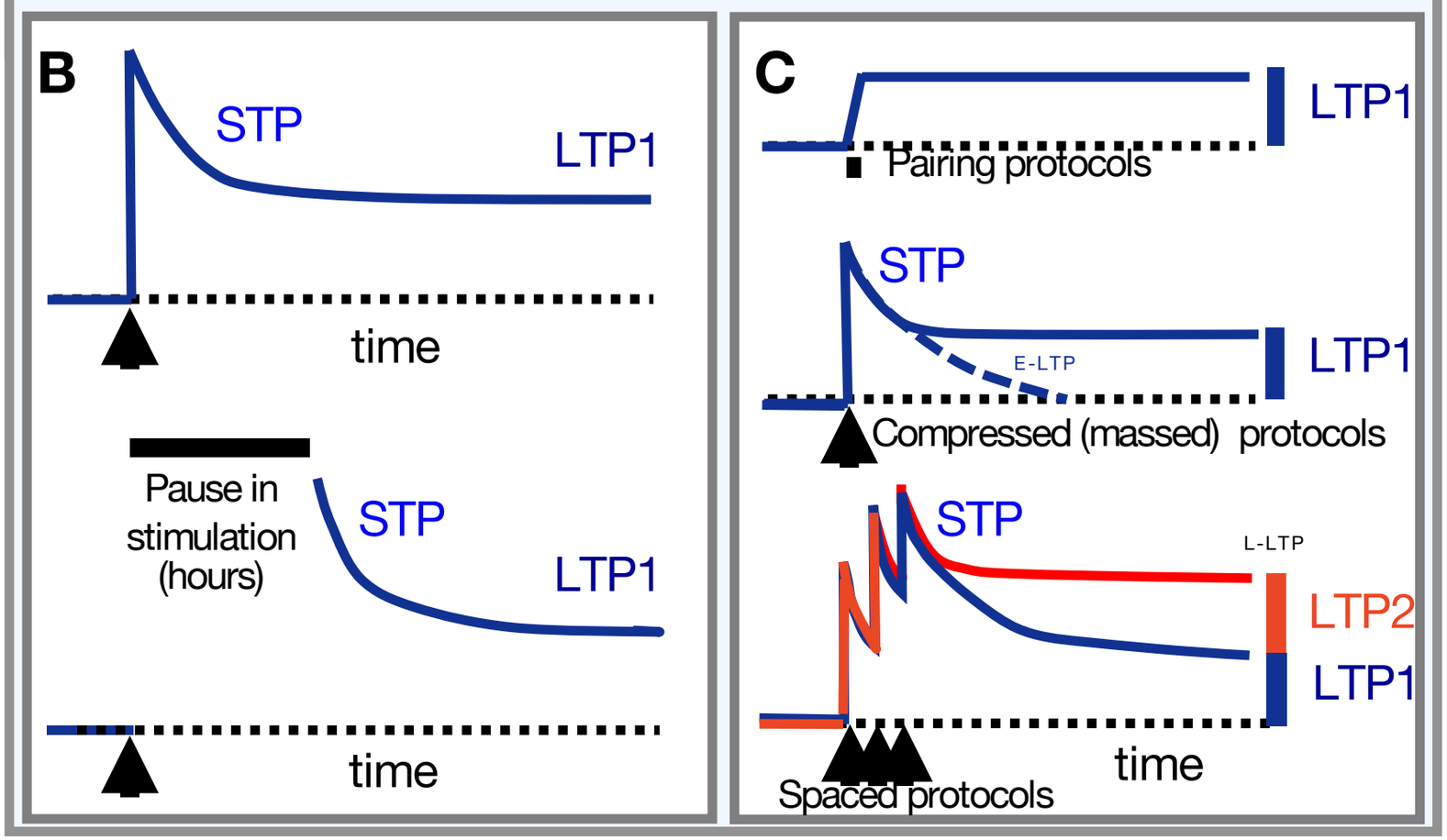
Multiple phases of LTP (1990s)



Multiple phases of LTP (2018)



From: **Prof. Dr. Klaus G. Reymann** reymann@lin-magdeburg.de
Subject: AW: NEUROFOR.2017.0059.R1 - Decision Accept
Date: 20 June 2018 at 16:06
To: MORRIS Richard R.G.M.Morris@ed.ac.uk

Has the second mail arrived meanwhile?
K.

-----Ursprüngliche Nachricht-----
Von: MORRIS Richard <R.G.M.Morris@ed.ac.uk>
Gesendet: Mittwoch, 20. Juni 2018 17:05
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Thanks - and do you have the final submitted text and figures?

> On 20 Jun 2018, at 16:04, Prof. Dr. Klaus G. Reymann <reymann@lin-magdeburg.de> wrote:
>
> Aceptance letter below:
> K.
>
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> Von: Neuroforum <onbehalfof@manuscriptcentral.com>
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> Betreff: NEUROFOR.2017.0059.R1 - Decision Accept
>
> 31-May-2018
>
> Dear Dr. Reymann:
>
> I would like to thank you for submitting your manuscript to Neuroforum (NF). It is a pleasure to accept your manuscript entitled "Long-term potentiation in the hippocampus: discovery, mechanisms and function" in its current form for publication in NF.
>
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>
> Thank you for your contribution.
>
> Kind regards,
> Susanne Hannig
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